

Appeal No. 2002-0443
Application No. 09/139,375

The opinion in support of the decision being entered today was not written
for publication and is not binding precedent of the Board.

Paper No. 28

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte JUDAH FOLKMAN, HAROLD BREM
and H. PAUL EHRLICH

Appeal No. 2002-0443
Application No. 09/139,375

HEARD: November 19, 2002

Before WILLIAM F. SMITH, MILLS and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final

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1. A method to inhibit excessive scar formation and adhesions comprising administering to a patient in need thereof an effective amount of an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, penicillamine, and IL12.

6. A method for inhibiting surgical adhesions or burn contractions comprising administering to the site an effective amount of angiogenesis inhibitor selected from the group comprising thalidomide, fumigillin, collagenase inhibitors, penicillamine, and IL12.

10. A composition for application to a wound comprising a polymeric barrier or implant comprising an angiogenesis inhibitor selected from the group comprising thalidomide, fumigillin, collagenase inhibitors, penicillamine, and IL12 in a dosage formulation comprising a pharmaceutically acceptable carrier for topical application in an amount effective to prevent or inhibit formation of hypertrophic scars or keloid scars, adhesions or burn contractions.

11. A composition comprising an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, penicillamine, and cytokines in a pharmaceutically acceptable carrier for topical application of the inhibitor selected from the group consisting of an ointment, gel, spray, and paste.

The references relied upon by the examiner are:

Piacquadio	5,605,684	Feb. 25, 1997
Kuwano et al. (Kuwano)	5,629,340	May 13, 1997

Fulton, et al. (Fulton), "Silicone Gel Sheeting for the Prevention and Management of Evolving Hypertrophic and Keloid Scars," Dermatol. Surg., Vol. 21, pp. 947-951 (1995)

Arbiser et al. (Arbiser), "Angiogenesis and the skin: A Primer," J. Amer. Aca. Dermatol., Vol. 34, No. 3, pp. 486-497 (1996)

References cited by Merits Panel

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European Patent Application
Folkman et al. (Folkman)

EP 0 325 199

Jul. 26, 1989

Grounds of Rejection

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Kuwano in view of Fulton.

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Piacquadio in view of Fulton.

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Arbiser in view of Fulton.

We reverse these rejections.

Claims 6, 9, 10, 13-15 and 19 are newly rejected under 35 U.S.C. § 102(b) over Folkman, and claim 11 is newly rejected under 35 U.S.C. § 102(e) over Tu, pursuant to 37 CFR § 1.196(b).

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and

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and to the appellants' Brief and Reply Brief for the appellants' arguments thereagainst.

As a consequence of our review, we make the determinations which follow.

Background

Claim 1 is directed to a method to inhibit excessive scar formation and adhesions comprising administering to a patient in need thereof an effective amount of an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, penicillamine, and IL12. According to the specification, patients to be treated include those having experienced trauma, surgical intervention, burns and other types of injuries. The angiogenesis inhibitor is administered in an effective amount to decrease excessive scarring, defined as formation of high density tissue including cells and connective tissue, without preventing normal wound closure. Specification, page 3. The specification also indicates that collagenase inhibitors include metalloproteinases and tetracyclines such as minocycline, fungal and bacterial derivatives, such as fumagillol derivatives like TNP-470, and sulfated polysaccharides. Specification, page 7. Fumagillol is a derivative of fumagillin.

Other claims in the application address a method for inhibiting surgical adhesions or burn contractions comprising administering to the site an effective amount

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angiogenesis inhibitor in a pharmaceutically acceptable carrier for topical application (claim 11).

35 U.S.C. § 103

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Kuwano in view of Fulton.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

The examiner argues that Kuwano discloses that angiogenesis inhibitors are useful for the treatment of hypertrophic scar diseases and that these inhibitors can be

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part of wound healing by preventing or reducing the evolution of hypertrophic scars and keloids. Id.

The examiner summarizes (Answer, page 4), “[i]t would be obvious to the skilled artisan that [sic] to combine these two prior art teachings, especially since both of these are directed to treating the same ailment of inhibiting excessive scar production.”

In our view, the examiner has not presented sufficient evidence to support a prima facie case of obviousness of the claimed invention. To begin, the examiner has made our analysis in this case difficult by failing to treat each of the independent claims in the application separately.

Furthermore, Kuwano indicates that disorders associated with abnormal acceleration of angiogenesis include surgical disorders such as hypertrophic scar and proud flesh, and that the antirheumatoid agent tetrahyracortizol in combination with heparin has been found to be useful to treat such disorders. Kuwano describes that D-penicillamine is another known anti-rheumatoid agent used in chronic articular rheumatism which also has anti-angiogenic activity. Column 1, lines 52-60. Kuwano, however, indicates that most of the anti-rheumatoid agents have serious side effects and proposes new compounds, unrelated to penicillamine, which may be used as angiogenesis inhibitors to treat various diseases associated with abnormal acceleration

excessive scar formation or surgical adhesions, however it suggests that antirheumatoid agents have unwanted side effects. In our view, when Kuwano is read as a whole, it does not provide sufficient evidence to support a prima facie case of obviousness of a method of inhibiting excessive scar formation and adhesions (as part of the normal wound healing process), which comprises administering to a patient in need thereof an effective amount of an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, penicillamine, and IL12.

Thus, we do not find that Kuwano supports a prima facie case of obviousness of method claims 1 and 6. Nor do we find Kuwano in combination with Fulton supports a prima facie case of obviousness of composition claims 10 and 11. In addition to the infirmities of Kuwano, Fulton is relied on by the examiner for the disclosure of the use of silicone gel sheeting for the management of evolving hypertrophic and keloid scars. Fulton indicates that “silicone gel treatment also appeared to inhibit blood vessel neoangiogenesis as telangiectasias.”² Appellants acknowledge that silicone sheeting provides a mechanical barrier to adhesion formation, but argue that Fulton suggests a combination treatment of corticosteroids and silicone sheeting, and does not suggest combination with an angiogenesis inhibitor. Brief, pages 6-7.

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We agree with appellants that the examiner has failed to provide sufficient evidence to support a prima facie case of obviousness of the compositions of claims 10 and 11, based on the infirmities of Kuwano. The rejection over Kuwano in view of Fulton is reversed.

35 U.S.C. § 103

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Piacquadio in view of Fulton.

According to the examiner, Piacquadio discloses that inhibitors of angiogenesis are useful for the topical treatment of wound healing in skin with thalidomide. Answer, page 5. The examiner argues an “artisan would have been motivated to employ thalidomide to treat scar formation, since it is well established that ‘wound healing’ embraces the formation of scar tissue.” Id.

Piacquadio indicates that a topical treatment of thalidomide is useful for the treatment of surface wounds, inflammatory disorders, ophthalmic, mucosal, conjunctiva and other ocular disorders, ulcerations and lesions. Abstract and column 2, lines 33-41. The examiner acknowledges that Piacquadio is silent as to a composition where the angiogenesis inhibitor is in a controlled release formulation, however, finds that the

Again the examiner has made our job difficult in failing to address the rejection of each of the independent claims individually. For example, the examiner argues it would have been obvious to the skilled artisan “to combine these two prior art references since they are both directed to the same purpose,” citing In re Kerkhoven,³ however, Fulton is not necessary to support a rejection of claim 1. Answer, page 5.

Appellants argue that the examiner has not established a prima facie case of obviousness as Piacquadio fails to address the prevention of excessive scarring or formation of adhesions, as claimed. Brief, page 8. We agree. Piacquadio indicates that topically administered thalidomide speeds up healing of skin ulcers and lesions, but does not suggest using thalidomide to affect scar formation. Columns 3 to 4. We do not find that Piacquadio would have suggested to one of ordinary skill in the art at the time of the invention or an expectation of success that thalidomide could be used for the treatment of excessive scarring or formation of adhesions, as claimed. Nor do we find that Piacquadio describes the treatment of surgical adhesions or burn contractions (Claim 6), or a composition for wound healing which comprises both a polymeric barrier or implant and an angiogenesis inhibitor (Claim 10) or an angiogenesis inhibitor according to claim 11. In view of the discussion herein, we do not find the examiner has provided sufficient evidence in the prior art to support a prima facie case of

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35 U.S.C. § 103(a)

Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as obvious over Arbiser in view of Fulton.

The examiner relies on Arbiser for teaching various inhibitors of angiogenesis, such as acidic fibroblast growth factor. Answer, page 6. Table II on page 490 of Arbiser also lists thalidomide and IL12 as angiogenesis inhibitors. Answer, page 6. The examiner concludes, it would be obvious to the skilled artisan that to combine these two prior art teachings, “since these prior art references are both directed to the same purpose,” citing In re Kerkhoven. Id. The examiner argues that Arbiser provides motivation to utilize various inhibitors of angiogenesis to treat hypertrophic scars and keloids when angiogenesis is defective and uncontrolled. Id.

Appellants argue that Arbiser provides a general discussion of angiogenesis inhibitors but does not teach inhibitors of angiogenesis would have an effect on scarring and surgical adhesions. Brief, page 8. Appellants also argue Arbiser teaches that angiogenesis is necessary for wound healing. “Nowhere in the Abstract or in the remainder of the article does Arbiser teach the inhibitors of angiogenesis would have an effect on scarring, surgical adhesions or other abnormal development involving collagen deposition.” Brief, page 8. We agree that Arbiser fails to specifically teach that the

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silicone sheeting is provided by Fulton alone, or in combination with Arbiser. In our view, at best, Fulton provides an expectation of success with respect to corticosteroids incorporated in a silicone sheeting, but cannot be read to provide an expectation of success with respect to other compounds having different chemical structures.

We agree with appellants that Arbiser fails to teach or suggest that inhibitors of angiogenesis would have an effect on scarring, surgical adhesions or other abnormal development involving collagen deposition, and that Fulton fails to overcome the noted deficiencies of Arbiser.

After evidence or argument is submitted by the applicant in response to an obviousness rejection, "patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument." In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); see In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787 (Fed. Cir. 1984) ("All evidence on the question of obviousness must be considered, both that supporting and that rebutting the prima facie case."). On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention nonobvious in view of the cited references. The rejection of the claims for obviousness of the claimed invention, is reversed.

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over Folkman.

Claims 6, 9 and 19

Folkman describes the use of fumagillin⁴ for the treatment of vascular adhesions associated with surgery at page 2, lines 9-19 and page 3, lines 20-25. Therefore, Folkman anticipates a method for inhibiting surgical adhesions or burn contractions comprising administering to the site an effective amount of angiogenesis inhibitor selected from the group comprising thalidomide, fumigillin, collagenase inhibitors, penicillamine, and IL12, as set forth in claims 6, 9 and 19.

Claim 10 and 13-15

Claim 10 is directed to a composition for application to a wound comprising a polymeric barrier or implant comprising an angiogenesis inhibitor selected from the group comprising thalidomide, fumigillin, collagenase inhibitors, penicillamine, and IL12 in a dosage formulation comprising a pharmaceutically acceptable carrier for topical application in an amount effective to prevent or inhibit formation of hypertrophic scars or keloid scars, adhesions or burn contractions. Folkman describes the use of fumagillin

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to treat wounds at page 3, line 10. Folkman describes that the angiogenesis inhibitory activity of fumagillin is potentiated by sulfated polysaccharides. Page 5. Folkman, page 4, line 56- to page 5, line 1, indicates the methylcellulose disks incorporating fumagillin were implanted in a shell-less chorioallantoic membrane (CAM). Effective amounts of fumagillin are set forth at pages 3 and 5 (Table 2) of Folkman. Thus, Folkman anticipates the composition of claim 10 and 13 -15.

37 CFR § 1.196(b)

Claim 11 is newly rejected under 102(e) over Tu, pursuant to 37 CFR § 1.196(b).

Claim 11 is directed to a composition comprising an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, penicillamine, and cytokines in a pharmaceutically acceptable carrier for topical application of the inhibitor selected from the group consisting of an ointment, gel, spray, and paste. Upon interpretation of claim 11, it would appear that claim 11 would be anticipated by a cytokine composition, such as IL12 which is administered topically in the form of an ointment, gel, spray or paste.

Tu discloses and claims the administration of IL-12 topically (claim 5). Tu,

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upon administration to an animal form a solid or a gel in situ.” Column 10, lines 14-18. The patent to Tu resulted from an application filed in the United States on January 31, 1995, prior to appellants' filing date of August 25, 1997. Thus, Tu anticipates claim 11 as it describes the topical administration of IL12, which topical formulation may be in the form of a gel, in situ.

CONCLUSION

The rejection of Claims 1-21 under 35 U.S.C. § 103(a) as obvious over Kuwano in view of Fulton, the rejection of claims 1-21 under 35 U.S.C. § 103(a) as obvious over Piacquadio in view of Fulton and the rejection of claims 1-21 under 35 U.S.C. § 103(a) as obvious over Arbiser in view of Fulton are reversed.

Claims 6, 9, 10, 13-15 and 19 are newly rejected under 35 U.S.C. § 102(b) over Folkman and appellants' admissions in the background portion of the specification, page 7. Claim 11 is newly rejected under 35 U.S.C. § 102(e) over Tu, pursuant to 37 CFR § 1.196(b). Claims 1-5, 7-8, 12, 16-18 and 20-21 are pending and without rejection pursuant to this appeal.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR

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37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .

(2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

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No time period for taking any subsequent action in connection with this appeal
may be extended under 37 CFR § 1.136(a).

REVERSED AND 1.196(b)

WILLIAM F. SMITH)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
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